201-15562B

CONDENSED ROBUST SUMMARY

Existing Chemical	ID: 99-08-1
CAS No.	99-08-1
EINECS Name	3-nitrotoluene
EINECS No.	202-728-6
TSCA Name	Benzene, 1-methyl-3-nitro-
Molecular Formula	C7H7NO2

Number of Pages: 19

Reliability (profile): Reliability: without reliability, 1, 2, 3, 4
Flags (profile): Flags: SIDS

2. Physico-chemical Data ID: 99-08-1

2.1 Melting Point

Value:	15.5 degree C
Decomposition:	no
Sublimation:	no
Method:	other: handbook value
GLP:	no
Test substance:	m-nitrotoluene; purity not noted
Reliability:	(2) valid with restrictions
Flag:	Critical study for SIDS endpoint

(1)

2.2 Boiling Point

Value:	232 degree C at 1013 hPa
Decomposition:	no
Method:	other: handbook value
GLP:	no
Test substance:	m-nitrotoluene; purity not noted
Reliability:	(2) valid with restrictions
Flag:	Critical study for SIDS endpoint

(1)

2.4 Vapor Pressure

Value:	10 hPa at 89.7 degree C
Method:	other (measured): handbook value
GLP:	no
Test substance:	m-nitrotoluene; purity not noted
Reliability:	(2) valid with restrictions
Flag:	Critical study for SIDS endpoint

(2)

2.5 Partition Coefficient

log Pow: 2.45 at 25 degree C
Method: other (measured)
Year:
GLP: no
Test substance: m-nitrotoluene; purity not noted
Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint
(3)

log Pow: 2.358 at 20 degree C
Method: other (calculated): KOWWIN Program (v1.65)
Year: 1999
GLP: no
Test substance: molecular structure
Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint
(4)

2.6.1 Water Solubility

Value: 498 mg/L at 30 degree C
Qualitative: moderately soluble(>100-1000 mg/L)
Method: other: Handbook value
Test substance: m-nitrotoluene; purity not noted
Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint
(5)

Value: 419 mg/L at 20 degree C
Qualitative: moderately soluble (>100-1000 mg/L)
Method: other
Test substance: m-nitrotoluene; purity not noted
Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint
(6)

3.1.1 Photodegradation

Type: water
Light source: Sunlight
Light spect.: 313 - 366 nm
Conc. of subst.: .00001 mol/l at 4 degree C
DIRECT PHOTOLYSIS
Halflife t1/2: 2.6 hour(s)
Quantum yield: .02
Test substance: m-nitrotoluene; purity not noted
Method: Saturated solutions in distilled water were centrifuged at 15,000 rpm for 30 min. The supernatant was removed and

diluted to concentrations of 10-6 to 10-5 M in distilled water,natural waters and aqueous solutions of extracted natural humic materials. Triplicate solutions were exposed to mid-day sunlight and monochromatic light (313 and 366 nm).The pH was 5.5. Exposure times were varied, achieving approx. 30% reaction for each exposure. Dark controls were used in each run. The solutions were then analyzed by reverse phase HPLC. Dark controls showed no transformation during the periods required for the experiments, which in most cases were less than 1 day.

Year: 1986 GLP: no data

Test substance: m-Nitrotoluene (99-08-1), purity: not given. Sample was purchased from Aldrich.

Reliability: (2) valid with restrictions

Flag: Critical study for SIDS endpoint

(7)

Type: air

INDIRECT PHOTOLYSIS

Sensitizer: OH

Conc. of sens.: 1560000 molecule/cm3

Rate constant: .0000000000005808 cm3/(molecule * sec)

Degradation: 50 % after 18.4 day

Method: other (calculated): AOP Program v1.89

Year: 1999 GLP: not applicable

Test substance: molecular structure

Reliability: (2) valid with restrictions

Flag: Critical study for SIDS endpoint

(4)

Type: water

Light source: 150W xenon lamp

Light spect.: >320 nm

Conc. of subst.: 100 µmol/l at 30±1 degree C

INDIRECT PHOTOLYSIS

Sensitizer: TiO2

Conc. of sens.: 1 g/l

Initial reaction rate: 6.76 µmol/l-min at pH 3 and 6.21 µmol/l-min at pH 11 at a light intensity of 3.5 µmole photons/min

Method: The photochemical experiments were performed in cylindrical reaction vessels made of borosilicate glass. The reaction vessels were placed into suitable bores of a tempered aluminum block. The light beam was focused through a hole in the aluminum block onto the irradiation vessel. Solutions and suspensions were magnetically stirred (about 600 rpm). The optical pathway contained a shutter and an UGI filter to minimize radiation with wavelengths shorter than 320 nm. To determine the influence of light intensity, the photon flux was varied between 0.8 and 4.0 µmole photons/min using neutral density filters. All components were mounted on an optical bench. Aqueous stock solutions, containing 100 µmole/l of the organic compound, were prepared with diluted slufuric acid (pH 3) by sonification for several hours, depending on the solubility of the organics. The pH of these stock solutions was adjusted with KOH. Before irradiation, the appropriate quantity of a stock solution was added to a previously weighed amount of TiO2 resulting in a catalyst concentraion of 1 g/l. These suspensions were thoroughly stirred for at least thirty minutes. Samples of 5 ml suspension or solution were

transferred into the reaction vessels. The vessels were sealed and tempered in the aluminum block to 30±1 deg C for about 15 min before irradiation. Photon fluxes were measured by ferrioxalate actinometry. After the desired time of irradiation the samples were immediately centifuged. The rates of disappearance of a given organic compound were monitored by a high-performance liquid chromatograph (HPLC) equipped with a UV detector. The measurements were conducted by monitoring the absorption at 254 nm or 270 nm. Reverse-phase columns, 250 mm long, 4.6 mm i.d., packed with ODS Hypersil 5 µm were used for separation and analyses.

Year: 1995 GLP: no data

Test substance: m-nitrotoluene; described as obtained from a reputable supplier and purified before use

Remark: Initial rate of photolysis did not vary with pH. In the absence of TiO2, m-nitrotoluene was degraded within 30 minutes, with the reaction rate being one order of magnitude lower than with the sensitizer.

(27)

3.1.2 Stability in Water

Type: abiotic

Degradation: 18 % after 8 days at pH 7.4 and 25 degree C

Method: other: Canton, J.H. and Slooff, W., Ecotoxicol. Environ. Safety 6, 113-128 (1982).

Year: 1982 GLP: no data

Test substance: m-nitrotoluene; purity > 99.5%

Remark: Stability was determined in nonaerated standardized medium before biodegradation studies.

Reliability: (2) valid with restrictions

Flag: Critical study for SIDS endpoint

(8)

3.3.1 Transport between Environmental Compartments

Type: fugacity model level III

Media: air - biota - sediment(s) - soil - water

Method: other: EPIWIN Fugacity model level III

Year: 1999

Result:

	Distribution (percent)	Half-Life (hr)	Emissions (kg/hr)	Fugacity (atm)
Air	5.84	270	1000	1.77e-010
Water	30.4	900	1000	9.02e-010
Soil	63.5	900	1000	6.08e-009
Sediment	0.201	3.60e+003	0	7.88e-010

Persistence Time: 568 hr
Reaction Time: 1.14e+003 hr
Advection Time: 1.13e+003 hr
Percent Reacted: 49.6
Percent Advected: 50.4

Reliability: (2) valid with restrictions

Flag: Critical study for SIDS endpoint

(4)

3.5 Biodegradation

Type: aerobic
Inoculum:
Concentration: 25 mg/l related to DOC (Dissolved Organic Carbon)
Contact time: 28 day
Degradation: 93 % after 28 day
Result: inherently biodegradable
14 day 75 %
28 day 93 %
Test substance: m-nitrotoluene; purity not noted
Method: Pitter, P. Water Res. 10, 231-235 (1976), modified. Two steps: acclimation of a mixed microbial population to the test substance in a semi-continuous activated sludge system and a die-away test in closed flasks. The main difference from Pitter's method is that the initial composition of the sludge, at the beginning of the acclimation-adaptation period, consists of a 1:1 (v/v) mixture of activated sludge from a domestic sewage plant and a solution containing organic material extracted from river mud.
Year: 1976 GLP: no
Remark: With inoculum concentration of 10 mg/l of dry matter, degradation after 2 weeks, 75%; after 4 weeks, 93%. A 10-fold higher concentration of adapted sludge resulted in 100% oxidation in 1 week. Adaptation failed when activated sludge from a domestic sewage plant was used exclusively. Under these conditions, no biodegradation occurred in 4 weeks.
Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint

(9)

Type: aerobic
Inoculum: sludge samplings from different sewage plants, rivers, bays and a lake
Concentration: 100 mg/l related to Test substance
Degradation: 2 % after 14 day
Method: OECD Guide-line 301 C "Ready Biodegradability: Modified MITI Test (I)"
Year: 1974 GLP: no
Test substance: m-nitrotoluene; purity not noted

Remark: "Biodegradation test of chemical substance by microorganisms etc." stipulated in the Order Prescribing the Items of the Test Relating to the New Chemical Substance (1974, Order of the Prime Minister, Minister of Health and Welfare, the MITI No. 1). This guideline corresponds to "301C, Ready Biodegradability: Modified MITI Test I" stipulated in the OECD Guidelines for Testing of Chemicals (May 12, 1981).
Sludge conc. : 30 mg/l
Reliability: (1) valid without restriction
Flag: Critical study for SIDS endpoint

(10)

Type: aerobic
Inoculum: activated sludge, adapted
Degradation: <10% after 28 days

3. Environmental Fate and Pathways ID: 99-08-1

Result: not readily biodegradable
Method: Blok, J. Int. Biodeterior. Bull. 15, 57-63 (1979). Determination of the Biodegradability of Anionic Surface Active Agents, OECD, Paris (1971). Pitter, P., Water Res. 10, 231-235 (1976).
Year: 1979 GLP: no
Test substance: m-nitrotoluene; purity >99.5%
Remark: Biodegradation was studied in a semistatic (revised OECD test, 1971; Repetitive Die Away Test: Blok, 1979) and a dynamic system (Pitter test: Pitter, 1976). The half-life was greater than 28 days whether the inoculum was adapted or not.
(8)

4. Ecotoxicity ID: 99-08-1

AQUATIC ORGANISMS

4.1 Acute/Prolonged Toxicity to Fish

Type: flow through
Species: Pimephales promelas (Fish, fresh water)
Exposure period: 96 hour(s)
Unit: mg/l Analytical monitoring: yes
LC50: 25.6
Method: The study was conducted according to ASTM E 729-80, Standard Guide for Conducting Acute Toxicity Tests with Fishes, Macroinvertebrates, and Amphibians, 1980.
Year: 1980 GLP: no data
Test substance: m-nitrotoluene purchased from Aldrich Chemical Company, Milwaukee, WI; purity = 99%

Remark: pH was adjusted to approximate that of Lake Superior water (pH 7.8) with NaOH or HCL. Compound analyses were done by GLC: all exposure chambers at 0,24,48,72, and 96 hr.

Fathead minnows used in this experiment were 33 days old and were cultured at US EPA Environmental Research Laboratory, Duluth, MN and University of Wisconsin - Superior campus.

25 fish/concentration and control. Behavior and toxic signs were noted at 4,24,48,72 and 96 hours.
Affected fish lost schooling behavior, were hypoactive and lost equilibrium prior to death. Effect data were not recorded.

Test condition: temperature =25.3 degree C (+/-0.39);
dissolved oxygen = 7.6 mg/l; pH = 7.49;
hardness = 45.1 mg/l CaCO3; tank volume = 1 liter;
measured concentrations 4.44, 4.9, 7.1, 8.41, 10.5, 12.4, 17.5, 20.6, 30.7, 37.9 mg/l.
Reliability: (1) valid without restriction
Flag: Critical study for SIDS endpoint
(11)

Type: static
Species: Pimephales promelas (Fish, fresh water)
Exposure period: 96 hour(s)
Unit: mg/l Analytical monitoring: no
LC50: 32.5
Method: other: The study was conducted according to ASTM E 729-80, Standard Guide for Conducting Acute Toxicity Tests with Fishes, Macroinvertebrates, and Amphibians, 1980.
Year: 1980 GLP: no
Test substance: m-nitrotoluene obtained from Pfaltz and Bauer; purity > 95%
Method: Method is described fully in the publication. Method follows ASTM E 729-80, Standard Guide for Conducting Acute Toxicity Tests with Fishes, Macroinvertebrates, and Amphibians, 1980.
Remark: Study reliability = 1 in AQUIRE
Reliability: (1) valid without restriction
Flag: Critical study for SIDS endpoint

(12)

Type: static
Species: Pimephales promelas (Fish, fresh water)
Exposure period: 96 hour(s)
Unit: mg/l Analytical monitoring: no
LC50: 30
Method:
Year: GLP: no
Test substance: m-Nitrotoluene (99-08-1) , obtained from Curtis Matheson Scientific, Inc; purity: reagent grade
Method: The Committee on Methods for Toxicity Tests with Aquatic Organisms. 1975. Methods for acute toxicity tests with fish, macroinvertebrates, and amphibians. U.S. Environmental Protection Agency, Duluth, Minn. Ecological Research Series EPA-660/3-75-009. 67 p.

Result:	1hr	24hr	48hr	72hr	96hr	
LC50	43	30	30	30	30	(mg/l)

Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint

(13)

4.2 Acute Toxicity to Aquatic Invertebrates

Type: static
Species: Daphnia magna (Crustacea)
Exposure period: 48 hour(s)
Unit: mg/l Analytical monitoring: no
LC50 : 7.5 (5.6-10)
Test substance: m-nitrotoluene; purity > 98%
Method: NEN 6501, Determination of acute toxicity with Daphnia magna. Dutch Standardization Organization, Rijswijk, the Netherlands (1980), with slight modifications according to Van Leeuwen, C.J. et al., Aquatic toxicological aspects of dithiocarbamates and related compounds. Short-term tests. Aquat. Toxicol. 7, 145-164 (1985).
Year: 1980 GLP: no
Remarks: Tests were done with 25 organisms per liter in duplicate. Control groups also had 25 organisms per liter. The medium used was standard water, as follows (NPR 6503, 1980): $NaHCO_3$ 100 mg/l

	$CaCl_2 \cdot 2H2O$ 200 $KHCO_3$ 20 $MgSO_4 \cdot 7H2O$ 180 The pH was 8.4±0.1 and the temperature in the room was 20±0.5°C. A 12 h light/dark cycle was used. The medium was saturated with air before use, and the oxygen content did not decrease below 7.9 mg/l (85%). Mortality in controls did not exceed 10%. All daphnids used were <24 h old at the start of the experiments. Test material concentrations increased geometrically with a factor of 3.2.
Reliability:	(1) valid without restriction
Flag:	Critical study for SIDS endpoint

(14)

Type:	static
Species:	Daphnia magna (Crustacea)
Exposure period:	24 hours
Unit:	mg/l Analytical monitoring: no
LC50 :	35
Method:	according to Bringmann, G. and Kuhn, R., (1977)
Year:	1977 GLP: no
Test substance:	m-nitrotoluene; purity not noted
Remark:	The test medium was chlorine-free tap water. Temperature was 20-22°C; water hardness was 70 mg/l of CaCO3; dissolved oxygen was saturated; pH was 7.6 to 7.7. Daphnia were 24 h old. Study reliability = 1 in AQUIRE
Reliability:	(1) valid without restriction
Flag:	Critical study for SIDS endpoint

(15)

4.3 Toxicity to Aquatic Plants e.g. Algae

Species:	Chlorella pyrenoidosa (Algae)
Endpoint:	growth rate
Exposure period:	96 hour(s)
Unit:	mg/l Analytical monitoring: no
EC50:	14(10-19)
Test substance:	m-nitrotoluene; purity > 98%
Method:	OECD, 1984. Guidelines for testing of chemicals. Organisation for Economic Cooperation and Development, Paris, Guideline 201, with slight modifications according to Van Leeuwen, C.J. et al., Aquat. Toxicol. 7, 145-164 (1985).
Year:	1984 GLP: no
Remarks:	Static test. Medium used was standard water, as follows: $CaCl_2 \cdot 2H2O$ 35 mg/l $MgSO_4 \cdot 7H2O$ 75 K_2HPO_4 52 Citric acid 6 $NaNO_3$ 500 $Na_2CO_3 \cdot 10H2O$ 54 Ferricitrate 6 NH_4NO_3 330 $MnCl_2 \cdot 4H2O$ 1.18 H_3BO_3 2.9 $ZnCl_2$ 0.11

$CuSO_4 \cdot 5H2O$	0.08
$(NH_4) \cdot Mo_7 \cdot O_{24}$	0.018

Test material concentrations increased geometrically with a factor of 3.2. A control group was used. The 96 h EC50 for effects on the yield of C. pyrenoidosa populations was calculated according to Kooyman, S.A.L.M., Parametric analysis of mortality rates in bioassays. Water Res. 15, 107-119 (1981).

Study reliability = 2 in AQUIRE
Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint

(14)

5.1 Acute Toxicity ID: 99-08-1

5.1.1 Acute Oral Toxicity

Type: LD50
Species: rat
Strain: Wistar
Sex: male/female
Number of Animals: 10/sex/dose level
Vehicle: olive oil
Value: 2000 - 2200 mg/kg bw
Test substance: other TS: m-nitrotoluene; purity = 99%
Method: Statistical analyses were performed according to Miller, L.C. and Tainter, M.L., Proc. Soc. Exp. Biol. Med. 57, 261-264 (1944); and Bartlett, M.S., Suppl.I. Roy.Stat. 4, 137-170 (1937). Volume given was 1 ml per 200 g/b.w. Rats were weighed on Day 1 of the study. Rats were given a single dose by gavage and observed for 14 days. Behavior and signs of toxicity and mortality were recorded daily. Animals that died or were killed in a moribund state were weighed and then subject to necropsy.

Year: 1978 GLP: no
Remark:
Result: 2200 (+/-145) mg/kg b.w. for males;
2000 (+/-145) mg/kg b.w. for females

Mortalities

Dose, mg/kg	males	females
1000	0/10	0/10
1500	1/10	2/10
2000	4/10	5/10
2500	6/10	7/10
3000	8/10	8/10
4000	10/10	10/10

All rats died within 2 days. At toxic doses, all rats had the same signs. Immediately after dosing, they were very agitated and made several circuits of their cages before tucking their heads between their front paws. Their respiratory rates

increased, and they had convulsions that lasted a very short time. This was followed by depression and general atony.
Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint
(16) (17)

5.1.2 Acute Inhalation Toxicity

Type: LC50
Species: rat
Strain: Sprague-Dawley
Sex: male
Number of Animals: 10
Vehicle: none
Exposure time: 4 hour(s)
Value: > 157 ppm
Test substance:
Method: Finney, D.J., Probit Analysis, 2nd ed, King Review Press (1952).
Year: 1977 GLP: no
Remark: There were no deaths during exposure or during the 14 day observation period. All animals gained weight; there were no gross lesions attributed to exposure. 157 ppm was 77% of saturation.
Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint
(18)

Type: LC50
Species: mouse
Strain: CF1
Sex: male
Number of Animals: 10
Vehicle: none
Exposure time: 4 hour(s)
Value: > 151 ppm
Test substance:
Method: Finney, D.J., Probit Analysis, 2nd ed, King Review Press (1952).
Year: 1977 GLP: no
Remark: There were no deaths during exposure or during the 14 day observation period. All animals gained weight; there were no gross lesions attributed to exposure. 151 ppm was 74% of saturation.
Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint
(18)

5.1.3 Acute Dermal Toxicity

Type: LD50
Species: rabbit
Strain: New Zealand white
Sex: female
Number of Animals: 3

5.1 Acute Toxicity ID: 99-08-1

Vehicle: none
Value: > 20000 mg/kg bw
Test substance: other TS: m-Nitrotoluene (99-08-1), purity not noted
Method:
Year: 1977 GLP: no

Remark: Doses were kept in contact with the skin for 24 hours and the rabbits then observed for 14 days. No observable toxic effects were seen. All rabbits gained weight normally during the 14 day observation period.
Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint

(18)

5.4 Repeated Dose Toxicity

Species: rat Sex: male/female
Strain: F344/N
Route of admin.: oral feed
Exposure period: 13 w
Frequency of treatment: daily
Post. obs. period: no
Doses: 625,1250,2500,5000,10000 ppm (=ca. 47,94,188,375,750 mg/kg bw)
Control Group: yes, concurrent no treatment
LOAEL: 625 ppm
Method: Rats were observed twice a day for mortality and moribundity; body weights, feed consumption, and clinical signs were recorded weekly. Body weights and clinical signs were also recorded at necropsy. Hematological and clinical chemistry endpoints included hematocrit, hemoglobin, erythrocytes, mean cell volume, mean cell hemoglobin, mean cell hemoglobin concentration, platelets, reticulocytes, leukocytes, segmented neutrophils, lymphocytes, monocytes, eosinophils, nucleated erythrocytes/100 leukocytes, urea nitrogen, creatinine, total protein, methemoglobin, alkaline phosphatase, alanine aminotransferate, creatine kinase, sorbitol dehydrogenase, and bile acids. The following tissues were examined histologically: gross lesions, tissue masses or suspect tumors and regional lymph nodes, skin, mandibular and mesenteric lymph nodes, mammary glands with adjacent skin, salivary glands, thigh muscle, ileum, colon, cecum, rectum, liver, femur (to include diaphysis with marrow cavity and epiphysis), thymus, trachea, lungs and bronchi, heart, thyroid, parathyroids, esophagus, stomach, duodenum, jejunum, pancreas, spleen, kidneys, adrenal glands, urinary bladder, seminal vesicles, prostate, testes, epididymides, ovaries, uterus, nasal cavity and nasal turbinates, brain with stem, pituitary, preputial or clitoral glands. The following organs were weighed at termination of the study: heart, liver, lungs, right kidney, thymus, and right testicle.
Statistical methods: Organ and body weight data were analyzed using the parametric multiple comparisons procedures of Williams (1971; 1972) and Dunnett (1955). Clinical chemistry and hematology data were analyzed using the nonparametric multiple comparisons methods of Shirley (1977) and Dunn

(1964). Jonckheere's test (Jonckheere, 1954) was used to assess the significance of dose-response trends and to determine whether a trend-sensitive test (Williams, Shirley) was more appropriate for pairwise comparisons than a test capable ofdetecting departures from monotonic dose-response (Dunnett, Dunn). If the p-value from Jonckheere's test was greater than or equal to 0.10, Dunn's or Dunnett's test was used rather than Shirley's or Williams' test.

Year:	1992 GLP: yes
Test substance:	m-nitrotoluene; purity >96%
Remark:	10 rats/sex/group
Result:	No effects on survival; decreased wt gain and increased relative liver wt (M+F) at 10000 ppm; increased bile acids in M's at 5000 and 10000 ppm and in F's at 10000 ppm; mild increase in ALT in F's at 2500, 5000 and 10000 ppm; increased relative kidney wt at 10000 ppm (M's) and 5000 ppm (F's); hyaline droplet nephropathy in M's at all dose levels; changes in hematology and clinical chemistry in both sexes at all doses, including increased methemoglobin at 10000 (M+F) and at 5000(M's); hemosiderin and/or congestion in the spleen in both sexes at 5000 and 10000 ppm. Testicular degeneration occurred in all M's at 10000 ppm, along with decreased epididymal sperm count and concentration. The length of the estrous cycle increased at 5000 and 10000 ppm, while the number of cycling animals decreased.
Reliability:	(1) valid without restriction
Flag:	Critical study for SIDS endpoint

(19) (20)

Species:	mouse Sex: male/female
Strain:	B6C3F1
Route of admin.:	oral feed
Exposure period:	13 w
Frequency of treatment:	daily
Post. obs. period:	no
Doses:	625,1250,2500,5000,10000 ppm (=ca. 101,187,375,750,1500 mg/kg bw)
Control Group:	yes, concurrent no treatment
LOAEL:	625 - 675 ppm
Method:	Mice were observed twice a day for mortality and moribundity; body weights, feed consumption, and clinical signs were recorded weekly. Body weights and clinical signs were also recorded at necropsy. Hematological and clinical chemistry endpoints included hematocrit, hemoglobin, erythrocytes, mean cell volume, mean cell hemoglobin, mean cell hemoglobin concentration, platelets, reticulocytes, leukocytes, segmented neutrophils, lymphocytes, monocytes, eosinophils, nucleated erythrocytes/100 leukocytes, urea nitrogen, creatinine, total protein, methemoglobin, alkaline phosphatase, alanine aminotransferate, creatine kinase, sorbitol dehydrogenase, and bile acids. The following tissues were examined histologically: gross lesions, tissue masses or suspect tumors and regional lymph nodes, skin, mandibular and mesenteric lymph nodes, mammary glands with adjacent skin, salivary glands, thigh muscle, ileum, colon, cecum, rectum,

liver, femur (to include diaphysis with marrow cavity and epiphysis), thymus, trachea, lungs and bronchi, heart, thyroid, parathyroids, esophagus, stomach, duodenum, jejunum, pancreas, spleen, kidneys, adrenal glands, urinary bladder, seminal vesicles, prostate, testes, epididymides, ovaries, uterus, nasal cavity and nasal turbinates, brain with stem, pituitary, preputial or clitoral glands. The following organs were weighed at termination of the study: heart, liver with gallbladder, lungs, right kidney, thymus, and right testicle. Statistical methods: Organ and body weight data were analyzed using the parametric multiple comparisons procedures of Williams (1971; 1972) and Dunnett (1955). Clinical chemistry and hematology data were analyzed using the nonparametric multiple comparisons methods of Shirley (1977) and Dunn (1964). Jonckheere's test (Jonckheere, 1954) was used to assess the significance of dose-response trends and to determine whether a trend-sensitive test (Williams, Shirley) was more appropriate for pairwise comparisons than a test capable ofdetecting departures from monotonic dose-response (Dunnett, Dunn). If the p-value from Jonckheere's test was greater than or equal to 0.10, Dunn's or Dunnett's test was used rather than Shirley's or Williams' test.

Year:	1992 GLP: yes
Test substance:	other TS: m-nitrotoluene; purity >96%
Remark:	10 animals/sex/group
Result:	no effects on survival; decreased food consumption, decreased wt gain in both sexes at 5000 and 10000 ppm;, increased relative liver wts in both sexes at all doses, no gross or microscopic liver lesions; increased relative lung wts in both sexes at 10000 ppm; no toxicity to reproduction system.
Reliability:	(1) valid without restriction
Flag:	Critical study for SIDS endpoint

(19) (20)

5.5 Genetic Toxicity 'in Vitro'

Type:	Ames test
System of testing:	Salmonella typhimurium TA98, TA100, TA1535, TA1537
Concentration:	0, 3.3, 10, 33, 100, 333ug/plate
Cytotoxic Conc.:	with and without metabolic activation: 333.0 ug/plate
Metabolic activation:	with and without
Result:	negative
Test substance:	m-nitrotoluene, purity >99%
Method:	Yahagi, T. et al, Cancer Lett 1, 91-96 (1975); Ames, B.N. et al, Mutat. Res. 31, 347-364 (1975). Both male Sprague-Dawley rat liver and male Syrian hamster liver used for metabolic activation. DMSO used as a solvent. A preincubation protocol was used. Positive response was a reproducible, dose-related increase whether 2X background or not. Positive controls were 2-aminoanthracene for all strains in the presence of S9. In the absence of S9, 4-nitro-o-phenylenediamine was used for TA98, sodium azide for TA100 and TA1535, and 9-aminoacridine for TA1537. Three replicate plates were used for each of the two trials.
Year:	1975 GLP: no

Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint
(19) (21) (22)

Type: Cytogenetics assay
System of testing: Chinese Hamster ovary (CHO) cells
Concentration: 150, 300, 398, 437, 460, 483 ug/ml
Cytotoxic Conc.: see remarks below
Metabolic activation: with and without
Result: negative
Method: other: Galloway, S.M. et al., Environ. Mutagen. 7(1) 1-51 (1985)
One hundred cells per dose level were evaluated. The metabolic activation system was obtained from the livers of Sprague-Dawley rats induced with Aroclor 1254. Positive controls were triethylenemelamine in tests without S9, and cyclophosphamide with S9.
Year: 1985 GLP: no
Test substance: m-nitrotoluene, purity >96%
Remark: The top dose selected was estimated to reduce growth by 50%; cell growth and cell cycle kinetics information from the SCE test were also used to select doses.
Author's remarks: The aberration tests with and without S9 were negative whether cells were fixed at 11 hr or at 20 hr.
Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint
(19) (23) (24)

Type: Cytogenetics assay
System of testing: Chinese Hamster lung(CHL) cells
Concentration: 250 ug/ml was maximum dose tested
Cytotoxic Conc.: no information given
Metabolic activation: none
Result: negative; significant increase in polyploid cells
Method: not given; original publication is Ishidate Jr. M (Ed.), Chromosome Aberration Test In Vitro, L.I.C. Inc., Tokyo (1987).
Incubation time was 48 hr.
Year: 1987 GLP: no
Test substance: m-nitrotoluene, purity not given (26)

_ Type: Cytogenetics assay
System of testing: Human peripheral lymphocytes
Concentration: 0.002, 0.020, 0.10, and 0.50 mmol/l
Cytotoxic Conc.: no information given
Metabolic activation: none
Result: positive; significant increase in the ratio of the number of aberrant cells to the number of metaphase cells scored
Method: Preston, R.J. et al, Mutat. Res. 189(2), 175-183 (1987)

Year: 1987 GLP: no
Test substance: m-nitrotoluene, purity not given (28)

Type: Unscheduled DNA synthesis
Species: Rat
Strain: Fischer 344
Route of admin: gavage
Exposure period: single dose
Doses: 200 and 500 mg/kg
Result: negative
Method: Mirsalis, J.C. and Butterworth, B.E., Carcinogenesis (Lond.) 1: 621-625 (1980); Mirsalis, J.C. et al, Environ. Mutat. 4, 553-562 (1982). m-Nitrotoluene was dissolved in corn oil just before use and given at a volume of 0.2 ml/100 g body weight. Hepatocytes were isolated 12 hr after treatment by an EGTA-collagenase perfusion procedure. After a 90-min attachment period, hepatocytes were incubated in the presence of [^{3}H]thymidine for 4 hr and then in the presence of unlabeled thymidine for 14 hr. Positive control was dimethylnitrosamine.
Year: 1980 GLP: no
Test substance: m-nitrotoluene, purity 99% (29)

Type: Unscheduled DNA synthesis
Species: Male rat
Strain: Fischer 344
Route of admin: gavage
Exposure period: single dose
Doses: 100, 200 and 500 mg/kg
Result: negative
Method: Mirsalis, J.C. et al., Carcinogenesis 6: 1521-1524 (1985). m-Nitrotoluene was dissolved in corn oil before use and given at a volume of 5 ml/kg body weight. Hepatocytes were isolated 12 hr after treatment by an EGTA-collagenase perfusion procedure. After a 1.5 to 2 hr attachment period, hepatocytes were incubated in the presence of [^{3}H]thymidine for about 4 hr and then in the presence of unlabeled thymidine for 14 to 19 hr. Positive control was 2,6-dinitrotoluene.
Year: 1985 GLP: no
Test substance: m-nitrotoluene, purity >96% (30)

5.8 Toxicity to Reproduction

Type: Fertility
Species: rat Sex: male/female
Strain: Wistar
Route of admin.: gavage
Exposure Period: 24 w
Frequency of treatment: once/d 5 d/w
Premating Exposure Period
male: 12 weeks

female: 12 weeks
Duration of test: 6 months
Doses: 300 mg/kg bw in olive oil
Control Group: yes, concurrent vehicle
Test substance: m-nitrotoluene; purity = 99%
Method: Males and females were dosed for 3 months before mating and during mating. 5 Treated males were mated with 5 treated females, 5 treated males were mated with 5 control females, five control males were mated with 5 control females, and 5 control males were mated with 5 treated females. Females were dosed during gestation. They were then maintained without treatment until 2 months after parturition, at which time they were dosed for another 4 weeks. Males were also held from mating until 2 months after parturition, at which time they were also dosed for another 4 weeks. A satellite group of 2 control females that were mated with control males were dosed during lactation only. The behavior, growth curve, and mortality of the parental animals were recorded. Blood samples were taken for clinical pathology and hematology, and all rats were killed at 3 months after parturition. Rats were given a gross necropsy examination and tissues were processed and examined histopathologically.
Year: 1978 GLP: no

Remarks: The protocol is not a standard study, but it is sufficient as a screening study for effects on fertility. There were no adverse effects on reproduction.

Result: No effect on reproductive parameters.
General parental toxicity: Alopecia, hemosiderosis and congestion in the spleen, a slight decrease in the level of hemoglobin, and a slight increase in methemoglobin. No effects were seen on fertility.
Toxicity to offspring: When the dams were exposed during gestation, similar spleen effects were seen in the offspring at 3 months of age but were much less significant than in the parental animals. When dams were treated during lactation only, the offspring had no histopathological changes in any organs at three months of age.
Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint

(25) (17)

5.9 Developmental Toxicity/Teratogenicity

Species: rat Sex: male/female
Strain: Wistar
Route of admin.: gavage
Exposure period:
Frequency of treatment: daily, 5 days/week
Duration of test: 6 months
Doses: 300 mg/kg bw
Control Group: yes, concurrent vehicle
NOAEL Teratogen.: 300 mg/kg bw
Test substance: other TS: m-nitrotoluene; purity = 99%

Method: Males and females were dosed for 3 months before mating and during mating. 5 Treated males were mated with 5 treated females, 5 treated males were mated with 5 control females, five control males were mated with 5 control females, and 5 control males were mated with 5 treated females. Females were dosed during gestation. They were then maintained without treatment until 2 months after parturition, at which time they were dosed for another 4 weeks. Males were also held from mating until 2 months after parturition, at which time they were also dosed for another 4 weeks. A satellite group of 2 control females that were mated with control males were dosed during lactation only. The behavior, growth curve, and mortality of the parental animals were recorded. Blood samples were taken for clinical pathology and hematology, and all rats were killed at 3 months after parturition. Rats were given a gross necropsy examination and tissues were processed and examined histopathologically.
Exposure period: 3 months before mating, during 3 weeks of mating, gestation, and from month 2 to month 3 after parturition for treated females; 3 months before mating, during 3 weeks of mating, and from month 2 to month 3 after parturition for treated males; during lactation only for two control group females.

Year: GLP: no

Remark: The protocol is not a standard study, but it is sufficient as a screening study for developmental effects. There was no selective effect on the offspring.

Result: Maternal general toxicity: Increased spleen size and weight. Accumulation of hemosiderin pigment in the spleen, a result of hemolysis, and a proliferation of erythroblasts, a sign of regeneration of the blood. Congestion of the spleen capillary sinus.
Pregnancy/litter data: All the females, controls and treated, delivered from 10 to 15 pups of normal vitality and behavior. Mortality in the newborn pups was the same for controls and treated. Offspring exposed during gestation had either accumulation of hemosiderin pigment in the spleen or a proliferation of erthroblasts three months after birth. Pups exposed only during lactation had no signs of toxicity at three months of age.

Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint

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